Title: Amniotic fluid embolism: a rare complication of second trimester amniocentesis

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Short title

Amniotic fluid embolus immediately following amniocentesis

Keywords

amniotic fluid embolus; amniotic fluid syndrome; amniocentesis; anaphylaxis; anaphylactic shock; disseminated intravascular coagulopathy

Established Facts

1. Amniocentesis is an integral part of evaluation for fetal abnormal ultrasonographic findings.
2. Amniocentesis is rarely associated with adverse maternal and fetal outcome.

Novel Insights

1. This case reminds us to consider amniotic fluid embolism within the differential diagnosis of adverse reactions following amniocentesis when more common causes have been ruled out.
2. Anaphylactic reaction might mimic amniotic fluid embolism.
3. Severe coagulopathy diagnosed by laboratory tests, a part of the amniotic fluid embolism syndrome can be promptly confirmed by thromboelastography

Abstract

Amniotic fluid embolism occurring following diagnostic amniocentesis is extremely rare. Only two cases have been reported in the English literature over the past 55 years, the most recent one, approximately three decades ago. We present a case of amniocentesis at 24 weeks' gestation that was performed as part of evaluation of abnormal fetal ultrasound findings. Immediately following amniotic fluid aspiration, maternal hemodynamic collapse occurred, initially diagnosed and treated as anaphylactic shock. Shortly after initial therapy, coagulopathy was noted and amniotic fluid syndrome suspected. Rapid response restored maternal hemodynamic stability; however, the fetus had suffered fatal damage.

Introduction

Amniotic fluid embolism (AFE) is a rare obstetric catastrophe and one of the leading causes of maternal death accounting for 5-15% of all maternal deaths in the developed world [1]. The pathogenesis of AFE remains vague although several theories have been proposed including vessel obstruction by amniotic debris, anaphylaxis secondary to fetal material leak, and complement activation by a tissue factor present in the amniotic fluid. Accordingly, there are various terms used for description of this phenomenon, such as AFE, amniotic fluid syndrome, and anaphylactoid syndrome of pregnancy [1]. AFE classically presents with premonitory symptoms such as restlessness, numbness, agitation or tingling, and might rapidly progress to maternal collapse and fulminant coagulopathy. Nonetheless, the exact progression remains unpredictable and varies in combination and severity.

AFE should be considered in the differential diagnosis in any pregnant woman who suffers a sudden cardiovascular collapse or cardiac arrest, severe respiratory difficulty or hypoxia. If such events are followed by a coagulopathy that cannot be otherwise explained, AFE is the most likely diagnosis [2]. Furthermore, the use of diagnostic laboratory test to either confirm or refute the diagnosis of AFE is not recommended and therefore AFE remains a clinical diagnosis that does not require histologic confirmation, established by exclusion of other causes [1-3]. Treatment consists mainly of prompt supportive therapy to maintain hemodynamic stability and correction of coagulopathy.

Late mid trimester amniocentesis is a prevalent diagnostic procedure often critical to prenatal diagnosis, and is regarded as a relatively safe procedure. However, it poses potential risks including miscarriage, premature birth, infection, amniotic fluid leakage, and needle injury [4]. AFE is exceptionally rare. A PubMed search from January 1, 1966, through July 1, 2015 using search terms: "amniocentesis risks," "amniocentesis embolism," and "amniotic fluid embolism", revealed that two detailed cases of AFE after a diagnostic amniocentesis reported in the English literature during this period [5-6].

We present a case of AFE occurring immediately following second trimester amniocentesis.

Case Report

A 36-year old woman (gravida 2, para 1) was referred to our obstetric service at 24 weeks' gestation for amniocentesis due to abnormal ultrasound findings. Her past medical history included portal hypertension secondary to umbilical catheterization due to premature birth, portal vein thrombosis, esophageal varices, factor V Leiden homozygosity and controlled hypothyroidism. Her medical therapy included daily oral

propranolol 30 mg, subcutaneous enoxaparin 40 mg, and oral levothyroxine 100 mcg. Her first pregnancy was uncomplicated and she had an elective term cesarean delivery to avoid the consequences of potential esophageal varicose veins bleeding.

During current pregnancy, a routine 22-week fetal anatomical scan revealed mild polyhydramnios (maximal vertical pocket 100mm) [7] and non-visualization of fetal stomach throughout the exam and on repeat examinations. No additional sonographic abnormalities were detected. Following genetic consultation, the patient elected to undergo diagnostic amniocentesis, withholding enoxaparin treatment for 24 hours. At 24 weeks' gestation she had an ultrasound-guided single puncture amniocentesis, using sterile technique, 20 gauge needle, without local anesthesia, no trans-placental passage, and 25mL of clear amniotic fluid was aspirated. Upon removal of the needle, the patient complained of shortness of breath, became restless, and severe cutaneous erythema was noted. The rapid response team was called. Vital signs showed peripheral blood pressure of 80/40 mmHg, pulse rate of 130 beats per minute, and percutaneous oxygen saturation at room air of 88%. Physical examination revealed disseminated cutaneous edema and bilateral diffuse respiratory wheezing. The patient initial diagnosis was anaphylactic shock, treated by subcutaneous epinephrine 0.6mg and 100% oxygen via non-rebreathing mask. Hemodynamic stability was achieved after repeated epinephrine 10-20μg boluses for 15 minutes, ranitidine 50mg, phenergan 25mg, and continuous Ringer solution. Consecutively, circulatory and respiratory control was achieved within 30 minutes.

Laboratory data obtained from blood sample during the acute event were: hemoglobin 19.5gr/dL, hematocrit 55.6%; prothrombin time and partial thromboplastin time unmeasurable; fibrinogen levels were undetectable. A severe state of coagulopathy was further confirmed by no clot formation on thromboelastography (TEG) in >60 minutes,

as compared with the standard clot formation time of four to eight minutes. Despite the abnormal coagulopathy laboratory results, no clinical evidence of apparent bleeding was observed. At this point, the differential diagnosis of AFE sequence was raised. Repeat hemoglobin and hematocrit levels dropped and stabilized at between 10.0-11.0 gr/dL, and 29-31%, respectively. Coagulopathy was corrected using titrated fresh frozen plasma and cryoprecipitate because of the history of thrombotic complications and in accordance with her hereditary thrombophilia. Concurrent normal results evaluation included cultures, abdominal ultrasound, echocardiogram, and thoracic computed tomography. After maternal stabilization, the fetal evaluation revealed absent fetal movements, absent tone and no breathing episodes, compatible with fetal hypoxic injury. The patient opted for continuation of pregnancy. At 25 weeks' gestation spontaneous preterm premature rupture of membranes occurred (PPROM). Sonographic findings were fetal hydrops, enlargement of the ambient cistern, the Middle Cerebral Artery Peak Systolic Velocity (MCA PSV) was 0.7 MoM (Multiples of Median). Upon parental request and according to the Israeli law that allows in severe cases termination of pregnancy up to term and approval by the Ethics Committee a potassium-chloride injection feticide procedure and induction of labor were performed. After delivery, the placenta pathology showed no macroscopic or histologic signs of abruption or infection. Fetal autopsy was declined by patient; amniotic fluid karyotype disclosed no chromosomal abnormalities. At discharge the patient exhibited no evidence of physical sequelae. The patient entered into another pregnancy eighteen months later, gave birth at term to a healthy baby boy.

Discussion

Last reported three decades ago, this case represents a very uncommon circumstance of AFE sequence that occurred immediately following second trimester diagnostic

amniocentesis. As such, it was initially suspected to be an anaphylactic shock. Only in the minority of patients with AFE, severe disseminated coagulopathy occurs without any discernible clinical evidence of cardiopulmonary compromise [2]. Therefore, only upon revealing the severe presentation of laboratory coagulopathy, we felt that AFE remained the only plausible diagnosis having ruled out placental abruption, substance allergy, thromboembolism, cardiovascular disease and infection. Further appropriate treatment allowed us to save the mother, nonetheless unfortunately not the fetus. The high hematocrit and hemoglobin levels recorded during the acute event probably represent hemoconcentration, a result of third spacing and marked maternal edema. The rapid restoration of hemoglobin also supports this notion. The only risk factors for PPROM in our patient was amniocentesis [8]. The true cause of fetal hydrops in this case was not investigated as the patient presented with very early PPROM with such a grave prognosis and elected to have a termination of pregnancy. The Peak Systolic Velocity was within normal range, thus ruling out fetal-maternal hemorrhage as a cause of hydrops. Fetal autopsy was not performed, and therefore the definite cause for fetal hydrops could not be determined. Polyhydramnios is a well-known risk factor for AFE which was present in this patient.

To date, there are only two published cases of AFE diagnosis confirmed with the aid of thromboelastography [9-10]. In our case, thromboelastography was used for rapid confirmation of coagulopathy, thus confirming our diagnosis of AFE.

According to the American College of Obstetrics and Gynecologists (ACOG) the most common risk attributed to amniocentesis is the procedure-related loss rate which is suggested to be as low as 1 in 300–500, other complications occur infrequently and include transient vaginal spotting or amniotic fluid leakage and chorioamnionitis in less than 1 in 1,000 cases [4]. Nevertheless, implementation of non-invasive prenatal testing

(NIPT) as a screening test is expected to shift demand to late amniocentesis following abnormal late ultrasound findings.

Literature regarding AFE following amniocentesis is spare. The most recent case report was published almost three decades ago, in 1987. Dodgson et al [5] described amniocentesis performed at 28 weeks' gestation for relief of abdominal tension caused by polyhydramnios. Shortly after the procedure, the patient developed AFE and a transfusion exchange was initiated, saving the mother but not the fetus. Previous to this case report is a report by Hasaart et al [6] from 1983, they presented a case of AFE following amniocentesis in the third trimester to assess lung maturity. AFE occurred immediately; following prompt identification and therapy both mother and neonate survived with no permanent damage. Bell et al [11] noted only one maternal death due to of AFE out of 2000 diagnostic amniocentesis, however no additional details were supplied and other large series of amniocentesis do not report this complication [12-13]. Fairweather et al [14] in 1964 reported three women with rigors and unexplained fevers within 30 minutes to two hours following amniocentesis. They considered the possibility that this complication might have been due to a “minute liquor amnii embolism”.

We postulate that the lack of recent reports of AFE at early amniocentesis is a result of quantity rather than quality: a low amount of "anaphylactoid trigger" and limited area of amniotic fluid or placenta and maternal vascular contact. Our assumption is based on the evidence that the classic AFE sequence of events and severity is in part also quantity dependent [3].

In conclusion, we report this case to underscore the point that AFE is a rare complication of second trimester amniocentesis, and as illustrated in this case report, might initially resemble anaphylactic shock.

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